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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/29/2002 31

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/984,900	D'APICE ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b)

Status

1)☒ Responsive to communication(s) filed on *08 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,46-51,67 and 70-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,46-51 and 74-77* is/are allowed.

6)☒ Claim(s) *2,3,67,70-73,78 and 79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application)

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s) _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed 1-8-02 has been entered. Claims 80 and 81 have been canceled. Claims 1-3, 46 and 51 have been amended. Claims 1-3, 46-51, 67 and 70-79 are pending and under consideration.

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 2, 3, 78 and 79 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims read on naturally occurring cells expressing α-1-3 galactosyltransferase and a naturally occurring α-1-3 galactosyltransferase polypeptide.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 2, 3, 78 and 79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2, 3, 78 and 79 read on a host cell transformed with a nucleic acid molecule comprising a nucleic acid sequence that encodes a porcine polypeptide having α-1-3 galactosyltransferase (GT) activity and that hybridizes with the complementary sequence of nucleotides 90-1203 of SEQ ID No. 7 or a sequence corresponding to 90-1203 of SEQ ID No. 7 within the scope of degeneracy of the genetic code after a wash at 65^{0}C, 0.1% SDS and 0.05X to 0.5X SSC, and a porcine α-1-3 GT encoded by said nucleic acid molecule.

Nucleotide sequence that hybridizes with the complementary sequence of 90-1203 of SEQ ID No. 7 or a sequence corresponding to 90-1203 of SEQ ID No. 7 within the scope of degeneracy of the genetic code after a wash at 65^{0}C, 0.1% SDS and 0.05X to 0.5X SSC could encompass numerous unknown and unidentified nucleic acids that has polynucleotide sequence adding to 5', 3' and/or within the nucleotide sequence of SEQ ID No. 7, and the protein encoded by said nucleotide sequence has α-1-3 GT activity. The claims also encompass various variants of SEQ ID No. 10 and having α-1-3 GT activity.

The scope of the claim includes nucleic acid molecules encoding a genus of numerous structural variants of SEQ ID No. 10, and the genus is highly variant because a significant number of structural differences between genus members is permitted. A nucleotide sequence hybridizing to nucleotides 90-1203 of SEQ ID No. 7 can have a high homologous region with SEQ ID No. 7 but differ dramatically from SEQ ID No. 7 at the rest of the nucleotide sequence

and the protein encoded by said nucleotide sequence could be totally different from SEQ ID No. 10 and does not have α-1-3 GT activity. Therefore, structural features that could distinguish compounds in the genus from others in the nucleic acid or protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of SEQ ID No. 7 and 10 is insufficient to describe the genus.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of nucleic acid molecules encoding numerous variants of SEQ ID No. 10 or in possession of numerous variants of SEQ ID No. 10 and said variants having α-1-3 GT activities. Thus it is concluded that the written description requirement is not satisfied for the genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieve regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID Nos. 7 and 10, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2, 3, 78 and 79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid sequence having SEQ ID No. 7, a sequence corresponding to nucleotides 90-1203 of SEQ ID No. 7 within the degeneracy of the genetic code, and a porcine α-1-3 GT encoded by said nucleic acid sequence, does not reasonably provide enablement for a nucleic acid sequence that encodes a porcine polypeptide having α-1-3 GT activity and that hybridizes with the complementary sequence of nucleotides 90-1203 of SEQ ID No. 7 or a sequence corresponding to 90-1203 of SEQ ID No. 7 within the scope of degeneracy of the genetic code after a wash at 65^{0}C, 0.1% SDS and 0.05X to 0.5X SSC, and a porcine α-1-3 GT encoded by said nucleic acid sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 2, 3, 78 and 79 read on a host cell transformed with a nucleic acid molecule comprising a nucleic acid sequence that encodes a porcine polypeptide having α-1-3 galactosyltransferase (GT) activity and that hybridizes with the complementary sequence of nucleotides 90-1203 of SEQ ID No. 7 or a sequence corresponding to 90-1203 of SEQ ID No. 7 within the scope of degeneracy of the genetic code after a wash at 65^{0}C, 0.1% SDS and 0.05X to 0.5X SSC, and a porcine α-1-3 GT encoded by said nucleic acid molecule.

Nucleotide sequence that hybridizes with the complementary sequence of nucleotides 90-1203 of SEQ ID No. 7 or a sequence corresponding to 90-1203 of SEQ ID No. 7 within the scope of degeneracy of the genetic code after a wash at 65^{0}C, 0.1% SDS and 0.05X to 0.5X SSC

could encompass numerous unknown and unidentified nucleic acids that has polynucleotide sequence adding to 5', 3' and/or within the nucleotide sequence of SEQ ID No. 7, and the protein encoded by said nucleotide sequence has α-1-3 GT activity. The claims also encompass various variants of SEQ ID No. 10 and having α-1-3 GT activity.

The specification fails to provide adequate guidance for the regions or specific amino acids within SEQ ID No. 10 where mutations or variations would be tolerated without any change of the functional characteristic of said polypeptide and regions where they would not be tolerated. It was well known in the art that amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for

prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). In view of the lack of detailed information regarding the structural and functional requirements of the polypeptide of SEQ ID No. 10 and its variants, and the unpredictability of polypeptide function from mere amino acid sequence, it would be unpredictable whether the polypeptide variants of SEQ ID No. 10 would still retain the biological function of SEQ ID No. 10, i.e. porcine α-1-3 GT activity.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

7. Claims 2, 67, 70-73 and 78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a host cell transformed with a nucleic acid molecule comprising SEQ ID No. 7 *in vitro* or a porcine cell comprising at least one disrupted α-1-3 galactosyltransferase (GT) gene *in vitro*, wherein prior to disruption said gene encodes a porcine α-1-3 GT with amino acid sequence of SEQ ID No. 10, does not reasonably provide enablement

for a host cell transformed with a nucleic acid molecule comprising SEQ ID No. 7 *in vivo* or a porcine cell comprising at least one disrupted α-1-3 galactosyltransferase (GT) gene *in vivo*, wherein prior to disruption said gene encodes a porcine α-1-3 GT with amino acid sequence of SEQ ID No. 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 67 and 70-73 read on a porcine cell comprising at least one disrupted α-1-3 galactosyltransferase (GT) gene *in vitro* and *in vivo*, including a porcine cell with disrupted α-1-3 GT gene in a transgenic animal, such as a pocine, and a porcine cell with disrupted α-1-3 GT gene in a subject via gene therapy *in vivo*.

The specification discloses the purification of human anti-gal antibody, inhibition of human serum-induced lysis of porcine cells by sugars, e.g. melibiose, galactose, or by depleting anti-gal antibody in the serum, characterization of porcine α-1,3 GT gene, preparation of DNA construct containing interrupted mouse α-1,3 GT gene (pNeoαGT10.8B), production of α-1,3 GT homologous knockout mice by injecting mouse ES cells transfected by pNeoαGT10.8B into blastocyst and confirm the lack of the galactose α-1,3 galactose epitope in said knockout mice by anti-gal and IB4 lectin binding assay, and the resistance of spleen cells from knockout mice to lysis by human serum.

The specification fails to provide adequate guidance and evidence for producing a transgenic animal, such as a transgenic pocine, having disrupted α-1-3 GT gene in its genome and the resulting phenotype of said transgenic animal, such as a transgenic porcine.

The state of the art in the fields of transgenic animal at the time of the invention was unpredictable, the transgene expression and physiological results of such expression is not always accurately predictable. For example, the incidence of expression of the same fusion genes is much higher in transgenic mice than in pigs, introduction of human growth hormone transgene in mouse results in mammoth mouse phenotype, whereas introduction of same transgene into pigs results in several health problems, including lameness, lethargy, gastric ulcers, and anoestrous gilts (Palmiter et al., 1983, Science, Vol. 222, p. 809-814 (e.g. abstract); Pursel et al. 1990, J. Reprod. Fert., Suppl. Vol. 40, p. 235-245 (e.g. abstract, V)). Similarly, it is unpredictable for generating transgenic animals harboring disrupted α-1-3 GT gene. Wu et al., 1997 (Methods in Gene Biotechnology, CRC Press, Boca Raton, p. 339-365) pointed out that the approach of using ES cells carrying a single-copy mutation of a specific gene to generate knockout transgenic animal is time-consuming and costly to obtain homozygous or double-knockout mice, and another major concern is the potentially lethal effect of the targeted gene. In some cases, gene knockout results in early death of embryos and young animals, or morphologically and functionally abnormal offsprings such as blind and/or handicapped animals. Further, Sigmund, June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of

transgenic or gene-targeted animals. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (abstract). In view of the inherent unpredictability of the phenotype of a transgenic animal, such as transgenic pocine, and the lack of availability of embryonic stem cells for species other than mouse, it would require one skilled in the art at the time of the invention undue experimentation to generate a transgenic animal, such as a transgenic pocine, having a porcine cell containing a disrupted α-1-3 GT gene in its genome and a particular phenotype.

The specification also fails to provide adequate guidance and evidence for producing a porcine cell with disrupted α-1-3 GT gene in a subject via gene therapy *in vivo*.

The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma

(Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA are all important factors for a successful gene therapy (e.g. bridging pages 81-82).

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claims 2 and 78 read on a host cell, *in vitro* or *in vivo*, transformed with a nucleic acid molecule comprising a nucleic acid sequence that encodes a porcine polypeptide having α-1-3

galactosyltransferase (GT) activity and that hybridizes with the complementary sequence of nucleotides 90-1203 of SEQ ID No. 7 or a sequence corresponding to SEQ ID No. 7 within the scope of degeneracy of the genetic code after a wash at 65^{0}C, 0.1% SDS and 0.05X to 0.5X SSC. Similarly, claims 2 and 78 are rejected under 35 U.S.C. 112 first paragraph for the reasons as discussed for claims 67 and 70-73.

Conclusion

8. Claims 2, 3, 67, 70-73, 78 and 79 are rejected. Claims 1, 46-51 and 74-77 are in condition of allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

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